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Direct 1,1-Bisphosphonation of Isocyanides: Atom- and Step-Economical Access to Bisphosphinoylaminomethanes

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Cite This: *ACS Omega* 2021, 6, 8495−8501

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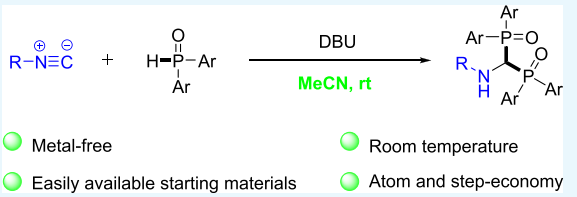
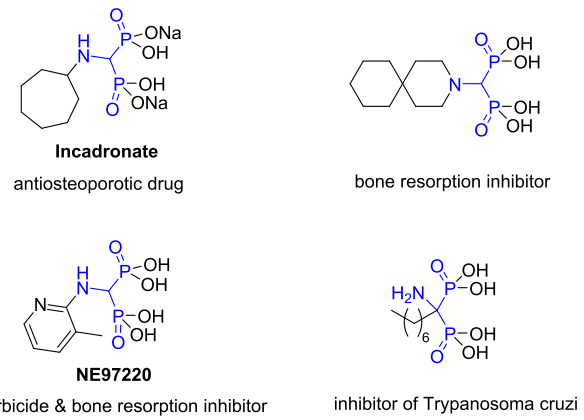
ABSTRACT: An atom- and step-economical strategy for the synthesis of bisphosphinoylaminomethanes is reported. This metal-free bisphosphinylation reaction proceeded smoothly through a base-mediated direct 1,1-bisphosphonation of phosphine oxides and isocyanides under mild conditions. The present method offers a facile, efficient, and general approach to a broad range of bisphosphinoylaminomethane derivatives in moderate to good yields.



INTRODUCTION

Organic phosphorus compounds have shown great diversity and wide applications in organic chemistry, which are applied to many fields ranging from the pharmaceutical industry to organometallic catalysis.[1−4] In particular, bisphosphorous aminomethane derivatives have attracted considerable attention owing to their unique biological and medicinal activities. As shown in Scheme 1, several bisphosphorous aminomethane-based pharmaceuticals are used as clinical drugs to treat osteoporosis, hypercalcemia, and Paget's disease.[5] Also, some of them exhibit various intriguing biological activities such as herbicidal, antibacterial, and antiparasitic properties.[6] Therefore, the remarkable activities of these compounds have stimulated a great effort to develop efficient synthetic methodologies. However, efficient synthetic methods for these bisphosphorus compounds, especially for bisphosphinoylaminomethane derivatives, are limited.[7] As shown in Scheme 2a, in 2006, Han and Hirai[8] reported a rhodium-catalyzed direct insertion of isocyanides to P(O)−H bonds for the synthesis of bisphosphinoylaminomethane. In 2017, Schmidt and Basiouny[9] developed a double hydrophosphinylation reaction of primary alkyl nitriles by using an α-metalated *N*,*N*-dimethylbenzylamine supported homoleptic lanthanum(III) complex La(Dmba)$_3$ as a catalyst (Scheme 2b). Very recently, Li and co-workers[10] constructed the bisphosphinoylaminomethane fragment *via* a cascade double nucleophilic addition, H_2S elimination, and in situ imine reduction of phosphine oxides and isocyanides (Scheme 2c). It was found that, in the previous reports, a noble or complexed metal catalyst should be used, high temperature and long reaction time were always necessary, and the substrate scope was sometimes limited. From economic or environmental friendly perspective, developing a general and green approach for the construction of bisphosphinoylaminomethanes would be highly desirable.

Scheme 1. Representative Bisphosphorous Aminomethane Derivatives



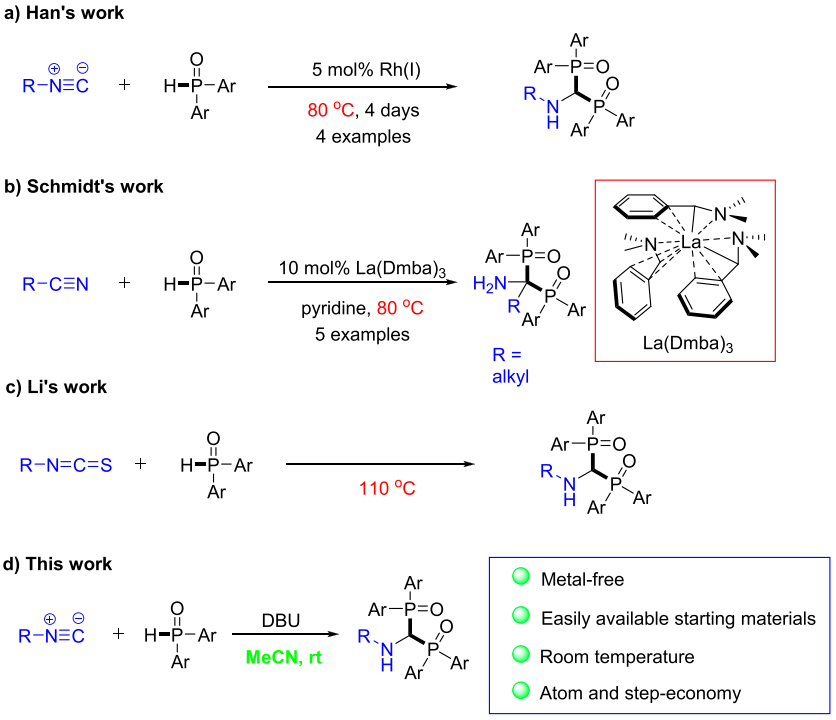
Isocyanides are important building blocks in modern organic synthesis, which have been widely employed in the construction of various nitrogen-containing compounds because they are easy to handle and exhibit high reactivity.[11,12] Given our continuing interest in isocyanide chemistry,[13] herein, we reported a highly efficient and straightforward isocyanide-based formal multicomponent reactions,[14] which provide an atom- and step-economical strategy for preparing bisphosphinoylaminomethane derivatives under mild conditions(Scheme 2d).

Results and Discussion. Initially, we investigated the reaction of 2-isocyanoacetophenone **1a** with phosphine oxide

Received: January 16, 2021
Accepted: February 1, 2021
Published: March 17, 2021

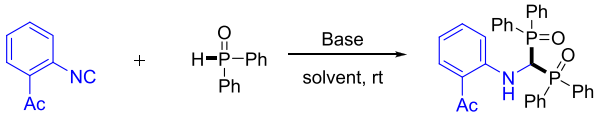
https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501

Scheme 2. (a−d) Synthesis of Bisphosphonaminomethane Derivatives



2a in 2 mL of DMSO at room temperature in the presence of DBU. To our delight, the desired product **3a** was formed in 83% yield (Table 1, entry 1). Encouraged by this promising result, we further tried the reactions by screening different bases. The desired product was obtained in moderate to good yields when some other organic bases were employed (Table 1, entries 2−6). The direct 1,1-bisphosphonation reaction proceeded smoothly in the presence of strong inorganic base (Table 1, entries 7−11). However, a trace amount of product was observed when weak inorganic bases (such as Cs_2CO_3 and K_2CO_3) were used (Table 1, entries 12−13). Next, a brief solvent-screening was carried out (Table 1, entries 14−20). It was found that the reaction showing a broad solvent tolerance and MeCN gave the best result (entry 17).

Table 1. Optimization of the Base[a,b]



1a **2a** **3a**

entry	base	solvent	yield (%)[b]
1	DBU	DMSO	83
2	Et_3N	DMSO	60
3	pyridine	DMSO	72
4	piperidine	DMSO	35
5	DIPEA	DMSO	58
6	DABCO	DMSO	41
7	NaOH	DMSO	50
8	KOH	DMSO	61
9	*t*-BuOK	DMSO	62
10	*t*-BuONa	DMSO	55
11	C_2H_5ONa	DMSO	67
12	Cs_2CO_3	DMSO	trace
13	K_2CO_3	DMSO	trace
14	DBU	DMF	72
15	DBU	DMA	70
16	DBU	MeCN	87
17	DBU	DCM	85
18	DBU	THF	81
19	DBU	toluene	77
20	DBU	EtOH	77

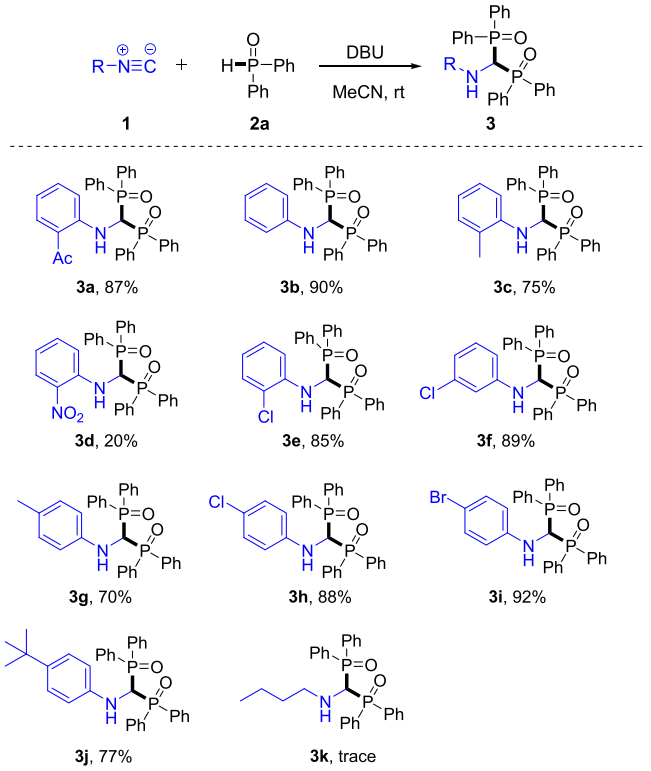
[a]Conditions: **1b** (0.5 mmol), **2a** (1.5 mmol), base (1.0 mmol), solvent (2 mL), at room temperature for 12 h. [b]Isolated yield.

With the optimized conditions in hand, we explored the substrate scope of isocyanides first. A broad range of isocyanides was examined in this double hydrophosphinylation reaction (Table 2). In general, *ortho*-, *meta*-, and *para*-substituted aromatic isocyanides are tolerated in the reaction and afforded the desired bisphosphorous aminomethane products in moderate to excellent yields. When halogen-substituted aromatic isocyanides were subjected with phosphine oxide **2a** under the standard reaction conditions, the desired products were obtained in 85−92% yields (Table 2; **3e**, **3f**, **3h**, and **3i**). It should be noticed that aromatic isocyanide bearing a NO_2 group has impaired the reactivity and decreased the yield (Table 2, **3d**). Unfortunately, only a trace amount of the desired product was observed when other alkyl isocyanide such as *n*-butyl isocyanide **1k** was used.

Next, we expanded the substrates with different diphenylphosphine oxides (Table 3). When the diphenylphosphine oxide substituted with a fluorine or phenyl group at the *para* position was employed under standard conditions, the desired bisphosphorous aminomethane products **4b** and **4c** were isolated in 85 and 81% yield, respectively. The reactions with the *meta*-substituted groups on P-reagents **1d**−**1f** furnished the corresponding products **4d**−**4f** in 90, 84, and 47% yields, respectively. Unfortunately, no desired product **4g** was observed when the *ortho*-methyl substituted P-reagent was used.

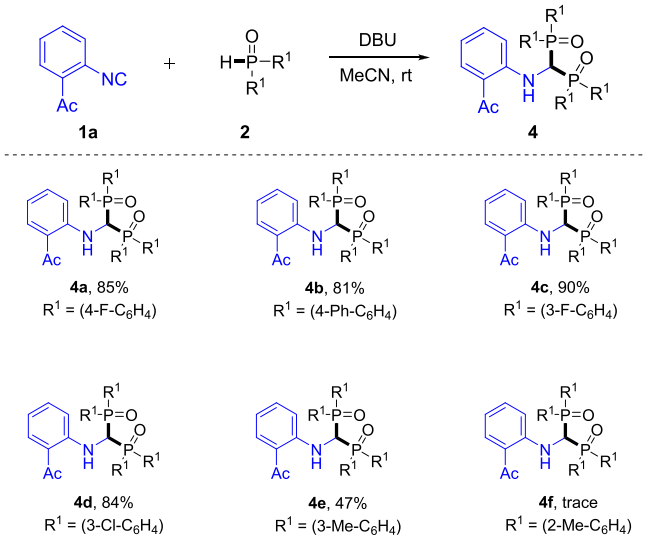
https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501

Table 2. Scope of Isocyanides[a,b]



[a]Reaction conditions: isocyanide **1** (0.5 mmol), **2a** (1.5 mmol), DBU (1.0 mmol), MeCN (2 mL), at room temperature, 12 h. [b]Isolated yield.

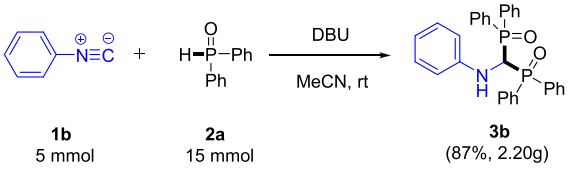
Table 3. Scope of Phosphine Oxides[a,b]



[a]Reaction conditions: isocyanide **1a** (0.5 mmol), diphenylphosphine oxides (1.5 mmol), DBU (1.0 mmol), MeCN (2 mL), at room temperature, 12 h. [b]Isolated yield.

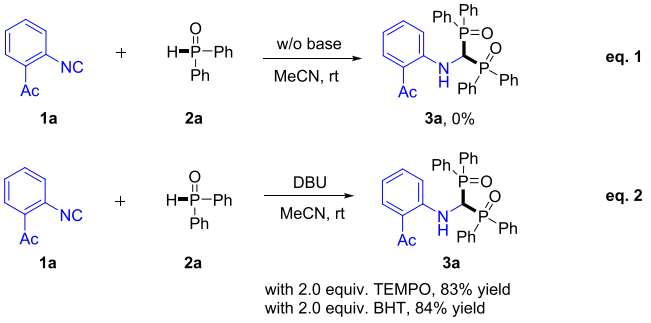
Furthermore, we tried to scale up the reaction to a gram scale. The reaction was well adapted for a gram scale and gave 2.20 g of bisphosphinoylaminomethane derivative **3a** in 87% yield (Scheme 3), which proves a simple and efficient approach for the synthesis of bisphosphinoylaminomethane derivatives.

Scheme 3. Scale-Up Synthesis



Some control experiments were carried out to gain some insights into the reaction. No desired product **3a** was observed when the double hydrophosphinylation reaction was treated in the absence of base (Scheme 4, eq 1). The bisphosphorous

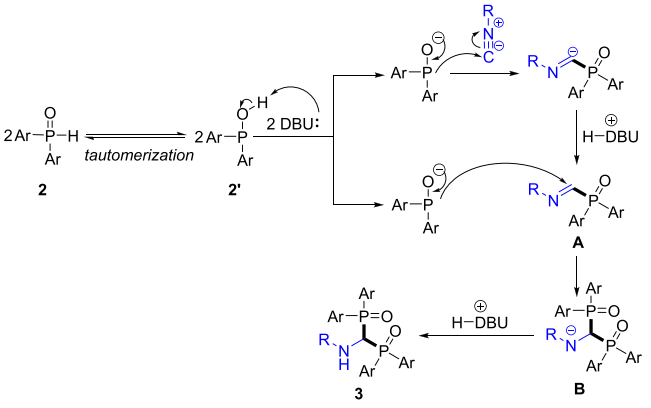
Scheme 4. Control Experiments



aminomethane product was isolated in 83 and 84% yield, respectively, when an excessive amount of free radical scavenger TEMPO or BHT was added under standard conditions (Scheme 4, eq 2). The results indicate that the reaction may not proceed with a free radical pathway, although our group[13g] and others[15] have reported the radical cascade addition reaction of phosphine oxides with aryl isonitriles before.

Based on the experiment results, a base-promoted double nucleophilic addition pathway was proposed for the 1,1-bisphosphonation reaction (Scheme 5). First, phosphite **2′**

Scheme 5. Plausible Mechanism



generated *via* tautomerization of phosphine oxide **2** was deprotonated by DBU. Then, the nucleophilic addition of isocyanide led to the imine intermediate **A**. The intermediate **A** would be attacked by another phosphite anion to generate intermediate **B**, which captured a hydrogen to give the final product.

https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501

CONCLUSIONS

In summary, we have developed an atom- and step-economical strategy for the synthesis of bisphosphinoylaminomethane derivatives in moderate to excellent yields by a base-mediated direct 1,1-bisphosphonation of phosphine oxides and isocyanides. The reaction proceeds under mild conditions and avoids using a noble and complexed metal catalyst. The simple and mild reaction conditions make the present method very practical and useful, offering a facile and efficient approach for the construction of bisphosphoryl derivatives.

EXPERIMENTAL SECTION

General Experimental Information. All the solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using a silica gel (200−300 mesh) with the indicated solvents. IR spectra were recorded on a spectrophotometer using a KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. The ^{1}H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and number of protons. High-resolution mass spectra were obtained using a high-resolution ESI-TOF mass spectrometer and high-resolution CI-TOF mass spectrometer.

General Procedure for the Synthesis of Arylisonitrile,.[13g13o] *Step 1: Formylation.* A total of 1.5 mL of formic acid and 3 mL of acetic anhydride were added to a 25 mL round-bottom flask, and then the flask was stirred in an oil bath at 55 °C for 2 h to give formic acetic anhydride. Aniline (10 mmol) and THF (20 mL) were added to a 100 mL round-bottom flask, and then the prepared formic acetic anhydride was added slowly. Afterward, the TCL thin layer chromatography plate was used for tracking and detection until the reaction was complete. Next, the reaction solution was placed in an ice-water bath, and a saturated sodium bicarbonate solution was slowly added until no bubbles were generated followed by extraction with ethyl acetate three times and drying with anhydrous magnesium sulfate and then concentrated under reduced pressure to give formamide for use.

Step 2: Dehydration. The prepared formamide was added into a 100 mL round-bottom flask, and the flask was evacuated and backfilled with argon three times followed by addition of dichloromethane (20 mL) and triethylamine (5 mL). The flask was cooled with an ice-water bath for 10 min, and then phosphorus oxychloride (1.5 mL) was added slowly. After the addition was complete, the reaction was stirred in the ice-water bath for 20 min. After that, the saturated carbon bicarbonate was added until no bubbles were generated. Then, the mixture was extracted with dichloromethane three times and dried over anhydrous magnesium sulfate. The product was isolated by silica gel column chromatography (petroleum ether/ethyl acetate V/V = 100:1−10:1).

General Procedure for the Synthesis of Diphenylphosphine.[10] A 100 mL three-neck round-bottom flask equipped with a reflux condenser was added 30.5 mmol of crushed magnesium scraps, and then a small amount of anhydrous tetrahydrofuran was added to immerse the magnesium scraps. A small amount of iodine was added into the flask and then the flask was heated to 65 °C in an oil bath until the iodine was completely dissolved, after which the diluted substituted bromobenzene was added slowly to keep the liquid in it slightly boiling status and continuously refluxed for 0.5−1.5 h after the dropwise addition of bromobenzene. After the reflux was completed, the flask was cooled to 0 °C in an ice-water bath, then 10 mmol of diethyl phosphate was slowly added thereto, and then the ice-water bath was reacted for half an hour. The ice-water bath was removed and stirred warmly, and the reaction was detected using a TCL plate. After quenching with dilute hydrochloric acid, the reaction solution was filtered with a Buchner funnel. The filtrate was extracted three times with ethyl acetate and dried over anhydrous magnesium sulfate. The product was isolated by silica gel column chromatography (petroleum ether/ethyl acetate V/V = 30:1−1:1).

General Procedure for Generation of 3 (3a as an Example). An over-dried reaction tube equipped with a magnetic stir bar was charged with **1a** (0.5 mmol, 1 equiv), **2a** (1.5 mmol, 3 equiv), and DBU (1.0 mmol, 2.0 equiv), and then MeCN (2.0 mL) was added into the mixture. Later, the reaction system was kept stirring at room temperature (25 °C) for 12 h. After that, the mixture was purified by column chromatography on a silica gel to afford the corresponding product **3a** as a green solid in 87% yield.

General Procedure for the Gram-Scale Synthesis of 3b. An over-dried round-bottom reaction flask (100 mL) equipped with a magnetic stir bar was charged with **1b** (5.0 mmol, 1.0 equiv), **2a** (15.0 mmol, 3 equiv), and DBU (10.0 mmol, 2 equiv), and then MeCN (20.0 mL) was added into the mixture. Later, the reaction system was kept stirring at room temperature (25 °C) for 12 h. After that, the mixture was purified by column chromatography on a silica gel to afford the corresponding product **3b** as a white solid in 87% yield.

*1-(2-((Bis(diphenylphosphoryl)methyl)amino)phenyl)-ethan-1-one (**3a**).* Green solid (238 mg, yield 87%). m.p.: 188 °C−190 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.61 (d, J = 10.8 Hz, 1H), 7.84 (m, 8H), 7.42 (m, 3H), 7.27 (m, 10H), 7.11 (m, 1H), 6.67 (m, 1H), 6.50 (m, 1H), 5.48 (br, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 200.6, 149.2, 134.6, 132.2, 131.9 (t, J = 4.8 Hz), 131.7 (t, J = 4.8 Hz), 131.2, 130.2, 128.3 (t, J = 6.0 Hz), 128.1 (t, J = 5.9 Hz), 119.4, 116.2, 112.5, 57.2, 27.7. HRMS (ESI) m/z: calcd for $C_{33}H_{29}NO_3P_2$ $[M + H]^+$: 549.1623, found: 549.1623.

*((Phenylamino)methylene)bis(diphenylphosphine oxide) (**3b**).* White solid (228 mg, yield 90%). m.p.:183 °C−185 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (d, J = 26.7 Hz, 8H), 7.63−7.04 (m, 12H), 6.87 (t, J = 6.3 Hz, 2H), 6.56 (t, J = 6.4 Hz, 1H), 6.29 (d, J = 7.2 Hz, 2H), 5.16 (q, J = 12.6 Hz, 1H), 4.66 (s, 1H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 146.0, 131.9, 131.8 (t, J = 4.7 Hz), 131.6 (t, J = 4.9 Hz), 128.8, 128.2 (m), 57.1. HRMS (ESI) m/z: calcd for $C_{31}H_{27}NO_2P_2$ $[M + H]^+$: 507.1517, found: 507.1516.

*((o-Tolylamino)methylene)bis(diphenylphosphine oxide) (**3c**).* White solid (195 mg, yield 75%). m.p.:182 °C−184 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (dd, J = 22.0, 14.0 Hz, 8H), 7.47−7.27 (m, 12H), 6.70 (d, J = 7.8 Hz, 2H), 6.21 (d, J = 8.0 Hz, 2H), 5.13 (q, J = 12.9 Hz, 1H), 4.57 (s, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 143.7, 132.0, 131.7 (t, J = 4.8 Hz), 131.6 (t, J = 4.8 Hz), 131.0, 128.3 (t, J = 5.9 Hz), 128.2 (t, J = 6.0 Hz), 126.6, 123.1, 118.5, 110.8, 56.6 (t, J = 64.1), 17.1. HRMS (ESI) m/z: calcd for $C_{32}H_{29}NO_2P_2$ $[M + H]^+$: 521.1674, found: 521.1674.

*(((2-Nitrophenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3d**).* Yellow solid (55 mg, yield

https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501

20%). m.p.:190 °C−192 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.57 (d, *J* = 10.4 Hz, 1H), 7.96−7.73 (m, 8H), 7.62−7.11 (m, 13H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.55 (t, *J* = 7.7 Hz, 1H), 5.46 (q, *J* = 9.6, 8.7 Hz, 1H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 145.1, 132.0, 131.7 (t, *J* = 4.6 Hz), 131.5−131.3 (m), 128.3−128.2 (m), 115.4, 110.7, 57.1. HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{26}N_2O_4P_2$ $[M + H]^+$: 552.1368, found: 552.1365.

(((2-Chlorophenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3e**). White solid (230 mg, yield 85%). m.p.:185 °C−187 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (dd, *J* = 27.8, 8.5 Hz, 8H), 7.46−7.25 (m, 12H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.48 (t, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.25 (d, *J* = 39.1 Hz, 2H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 145.2, 132.1, 131.8 (t, *J* = 4.6 Hz), 131.6−131.5 (m), 128.5−128.3 (m), 115.6, 110.8, 57.2. HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{26}ClNO_2P_2$ $[M + H]^+$: 541.1127, found: 541.1127.

(((3-Chlorophenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3f**). White solid (241 mg, yield 89%). m.p.:186 °C−188 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (dd, *J* = 17.1, 9.0 Hz, 8H), 7.58−7.11 (m, 12H), 6.81 (t, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 6.23 (d, *J* = 6.5 Hz, 2H), 5.16−4.99 (m, 1H), 4.97−4.78 (m, 1H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 147.2, 134.5, 132.1, 131.8 (t, *J* = 4.7 Hz), 131.5 (t, *J* = 4.6 Hz), 129.8, 128.4−128.3 (m), 118.9, 113.8, 112.1, 56.8 (t, *J* = 63.8). HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{26}ClNO_2P_2$ $[M + H]^+$: 541.1127, found: 541.1127.

((p-Tolylamino)methylene)bis(diphenylphosphine oxide) (**3g**). White solid (182 mg, yield 70%). m.p.:181 °C−183 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.81 (dd, *J* = 22.0, 14.0 Hz, 8H), 7.47−7.27 (m, 12H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.21 (d, *J* = 8.0 Hz, 2H), 5.13 (q, *J* = 12.9 Hz, 1H), 4.57 (s, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 143.7, 131.9 (t, *J* = 4.3 Hz), 131.6 (t, *J* = 4.8 Hz), 129.3, 128.3, 128.3−128.2 (m), 114.3, 57.6, 20.3. HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{29}NO_2P_2$ $[M + H]^+$: 521.1674, found: 521.1677.

(((4-Chlorophenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3h**). White solid (238 mg, yield 88%). m.p.:182 °C−184 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (dd, *J* = 15.6, 7.1 Hz, 8H), 7.45−7.29 (m, 12H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.24 (d, *J* = 8.3 Hz, 2H), 5.06 (q, *J* = 12.8 Hz, 1H), 4.76 (d, *J* = 4.3 Hz, 1H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 144.8, 132.1, 131.8 (t, *J* = 4.7 Hz), 131.5 (t, *J* = 4.8 Hz), 130.6 (t, *J* = 44.5 Hz), 128.7, 128.4−128.3 (m), 123.6, 115.1, 57.4 (t, *J* = 63.0 Hz). HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{26}ClNO_2P_2$ $[M + H]^+$: 541.1127, found: 541.1125.

(((4-Bromophenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3i**). White solid (269 mg, yield 92%). m.p.:186 °C−188 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (dd, *J* = 19.8, 8.2 Hz, 8H), 7.44−7.27 (m, 12H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.18 (d, *J* = 8.2 Hz, 2H), 5.05 (q, *J* = 12.6 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 145.2, 132.1, 131.8 (t, *J* = 4.6 Hz), 131.6−131.4 (m), 130.6 (t, *J* = 46.8 Hz), 128.4−128.3 (m), 115.5, 110.8, 57.2. HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{26}BrNO_2P_2$ $[M + H]^+$: 585.0622, found: 585.0620.

(((4-(tert-Butyl)phenyl)amino)methylene)bis-(diphenylphosphine oxide) (**3j**). White solid (217 mg, yield 77%). m.p.:180 °C−182 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.84 (dd, *J* = 37.0, 9.0 Hz, 8H), 7.49−7.26 (m, 12H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 8.5 Hz, 2H), 5.17 (q, *J* = 12.8 Hz, 1H), 4.49 (d, *J* = 9.9 Hz, 1H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 141.9, 131.9−131.6 (m), 130.8, 128.3−128.1 (m), 125.6, 114.4, 57.8, 33.8, 31.4. HRMS (ESI) *m*/*z*: calcd for $C_{35}H_{35}NO_2P_2$ $[M + H]^+$: 563.2143, found: 563.2140.

1-(2-((Bis(bis(4-fluorophenyl)phosphoryl)methyl)amino)-phenyl)ethan-1-one (**4a**). Green solid (264 mg, yield 85%). m.p.:175 °C−177 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.63 (d, *J* = 10.4 Hz, 1H), 7.88−7.74 (m, 8H), 7.54 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19−7.12 (2H), 7.04 (t, *J* = 8.4 Hz, 4H), 6.96 (t, *J* = 8.4 Hz, 4H), 6.60−6.56 (m, 1H), 5.34 (br, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 201.1, 165.3 (d, *J* = 253.4 Hz), 148.9, 134.9, 134.7−134.2 (m), 132.6, 125.8, 119.5, 116.9, 116.1 (t, *J* = 6.4 Hz), 116.0−115.8 (m), 115.6 (t, *J* = 6.4 Hz), 112.3, 27.9. HRMS (ESI) *m*/*z*: calcd for $C_{33}H_{25}F_4NO_3P_2$ $[M + H]^+$: 621.1246, found: 621.1245.

1-(2-((Bis(di([1,1′-biphenyl]-4-yl)phosphoryl)methyl)-amino)phenyl)ethan-1-one (**4b**). Green solid (350 mg, yield 81%). m.p.:173 °C−175 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.76 (d, *J* = 10.8 Hz, 1H), 8.09 (s, 4H), 7.94 (s, 4H), 7.55−7.53 (m, 4H), 7.42−7.36 (m, 24H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.04 (br, 1H), 6.50 (t, *J* = 7.6 Hz, 1H), 5.79 (br, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 200.8, 149.5, 144.6, 144.5, 139.6, 134.8, 132.4−132.1 (m), 128.9, 128.1, 127.1, 126.7 (t, *J* = 6.0 Hz), 119.5, 116.5, 113.4, 27.7. HRMS (ESI) *m*/*z*: calcd for $C_{57}H_{45}NO_3P_2$ $[M + H]^+$: 863.2875, found: 863.2872.

1-(2-((Bis(bis(3-fluorophenyl)phosphoryl)methyl)amino)-phenyl)ethan-1-one (**4c**). Green solid (280 mg, yield 90%). m.p.:174 °C−176 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.69 (d, *J* = 10.9 Hz, 1H), 7.76−7.72 (m, 2H), 7.67−7.35 (m, 10H), 7.31−7.07 (m, 6H), 6.79−6.40 (m, 2H), 5.44−5.34 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 201.0, 148.6, 134.8, 132.4, 130.5−130.2 (m), 127.5, 127.3, 119.8−119.5 (m), 119.1−118.5 (m), 117.0, 112.2, 57.4 (t, *J* = 63.8 Hz), 27.7. HRMS (ESI) *m*/*z*: calcd for $C_{33}H_{25}F_4NO_3P_2$ $[M + H]^+$: 621.1246, found: 621.1245.

1-(2-((Bis(bis(3-chlorophenyl)phosphoryl)methyl)amino)-phenyl)ethan-1-one (**4d**). Green solid (288 mg, yield 84%). m.p.:171 °C−173 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.68 (d, *J* = 10.9 Hz, 1H), 7.78−7.05 (m, 18H), 6.75−6.49 (m, 2H), 5.45−5.35 (m, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 201.1, 148.6, 134.8, 132.4, 130.7−130.5, 130.4−130.2 (m), 127.6−127.4 (m), 127.3−127.2 (m), 57.3 (t, *J* =)130.2, 130.1, 127.5, 127.1, 119.7, 119.6, 119.5, 119.4, 119.0, 118.7, 118.4, 116.9, 112.1, 57.3 (t, *J* = 65.0 Hz), 27.7. HRMS (ESI) *m*/*z*: calcd for $C_{33}H_{25}NO_3P_2$ $[M + H]^+$: 685.0064, found: 685.0062.

1-(2-((Bis(di-m-tolylphosphoryl)methyl)amino)phenyl)-ethan-1-one (**4e**). Green solid (142 mg, yield 47%). m.p.:176 °C−178 °C. ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.55 (d, *J* = 10.8, 1H), 7.73−7.66 (m, 2H), 7.61−7.50 (m, 4H), 7.53−7.48 (m, 2H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.22−7.07 (m, 9H), 6.75 (d, *J* = 8.6 Hz, 1H), 6.47 (t, *J* = 7.5 Hz, 1H), 5.50−5.40 (m, 1H), 2.34 (s, 3H), 2.20 (s, 6H), 2.15 (s, 6H). ^{13}C NMR (100 MHz, chloroform-*d*) δ 200.4, 149.2, 138.0 (t, *J* = 6.0 Hz), 137.7 (t, *J* = 5.8 Hz), 134.4, 132.6, 132.3−132.1 (m), 128.9 (t, *J* = 4.9 Hz), 128.5 (t, *J* = 5.1 Hz), 128.1 (t, *J* = 6.5 Hz), 127.9 (t, *J* = 6.4 Hz), 119.2, 116.0, 112.6, 57.2 (t, *J* = 59.7 Hz), 27.7, 21.3, 21.2. HRMS (ESI) *m*/*z*: calcd for $C_{37}H_{37}NO_3P_2$ $[M + H]^+$: 605.2249, found: 605.2249.

https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c00160.

^{1}H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21672157), PAPD, the Project of Scientific and Technologic Infrastructure of Suzhou (SZS201708), Natural Science Foundation of Jiangsu Province (BK20200874), Natural Science Foundation for Colleges and Universities in Jiangsu Province (20KJD150001), and Soochow University (Q410900620) for financial support. We thank Hai-Feng Yao in this group for repeating the results.

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https://dx.doi.org/10.1021/acsomega.1c00160
ACS Omega 2021, 6, 8495−8501